REMARKS

In the Office Action dated June 29, 2007, the Examiner refers to Applicants' amendment filed on May 3, 2007. (Office Action, page 1.) To clarify the record, Applicants' amendment was filed April 30, 2007, not May 3, 2007.

I. CLAIMS

Claims 1-6, 9, 12, 17, 21-23, 26-30 and 34 are pending in the application, with claim 1 being the sole independent claim. Claims 31-32 are currently withdrawn and are being maintained of record pending rejoinder or the filing of one or more divisional applications.[1]

II. CLAIMED INVENTION IS NOVEL AND NONOBVIOUS

Claims 1-6, 9, 12, 17, 21-23, 26-30 and 34 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over WO 99/18799A1 (Lorence '99) in view of WO 94/25627A1 (Lorence '94). (Office Action, paragraph 20.)

Claims 1-6, 9, 12, 17, 21-23, 26-30 and 34 are rejected under 35 U.S.C. § 102(a) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Pecora *et al.* (J. Clinical Oncology May 2002, 20(9):2251-2266) in view of Lorence '94. (Office Action, paragraph 24.)

Claims 1-6, 9, 12, 17, 21-23, 26-30 and 34 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over WO 00/62735A2 (Lorence '00) in view of Lorence '94. (Office Action, paragraph 29.)

All of the preceding rejections are respectfully traversed below.

Applicants appreciate and acknowledge that the Examiner has withdrawn the rejection of claims 1-5 and 34 over U.S. Patent No. 7,056,689 under 35 U.S.C § 102(e) and over U.S. Patent No. 7,056,689 in view of Lorence '94 under 35 U.S.C. § 103. (Office Action, the second paragraph 31.)

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[1] Applicants note that claims 31-32 are listed as rejected on page 1 of the Office Action, but believe this is a typographical error since these claims are also listed as withdrawn on page 2 of the Office Action.

A. Rejections Under 35 U.S.C. § 102

To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (*Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).) "The identical invention must be shown in as complete detail as is contained in the ... claim." (*Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989).) An anticipation rejection under 35 U.S.C. § 102 requires a showing that each limitation of a claim is found in a single reference, practice, or device. (*See In re Donohue*, 766 F.2d 531, 534 (Fed. Cir. 1985).)

> The subject matter encompassed by the present claims comprises, *inter alia*:
>
> wherein at least one cycle comprises administering sequentially two or more desensitization doses of the virus [to a subject] followed by administering one or more escalated doses of the virus, wherein . . . the amount of the virus in the second and any subsequent desensitization dose is greater than the amount of the virus in the preceding desensitization dose; and the amount of the virus in each of the one or more escalated doses is higher than the amount of virus in each of the desensitization doses.

(underlining, added.) Therefore, to anticipate the present claims, a single disclosure would have to describe, *inter alia*, (i) the administration of at least three different dose levels of virus, and (ii) the amount of virus in each of the at least three doses is greater than the previous dose of the at least three doses.

None of the documents, cited by the Examiner under the 35 U.S.C. § 102 rejection, disclose or suggest the feature of the claimed invention as described in the preceding paragraph. Therefore, the present claims are distinguishable over the cited documents because the cited documents do not set forth each and every claim element, either expressly or inherently. In other words, the cited documents do not describe all of the elements. Claims 2-5, 6, 9, 12, 17, 21-23, 26-30 and 34 depend from claim 1, and hence incorporate all of the features of claim 1. Therefore for the reasons discussed above, the claims are not anticipated by the cited references.

Applicants believe there may be a misunderstanding as to what dosing regimens are described in the cited documents. None of Lorence '94, Lorence 99, Lorence '00 nor Pecora *et*

al. disclose (i) the administration of at least three different dose levels of virus, and that (ii) the amount of virus in each of the at least three doses is greater than the previous dose of the at least three doses. Therefore, these documents do not disclose the administration of three doses with different amounts of virus, wherein the amount of the virus in the second and any subsequent desensitization dose is greater than the amount of the virus in the preceding desensitization dose; and the amount of the virus in each of the one or more escalated doses is higher than the amount of virus in each of the desensitization doses.

With regards to Lorence '99, the Examiner states,

> the claimed method cited in claims 1-5, 34 in Lorence R (B) (WO 99/18799A1) is also directed to use NDV for treating a tumor with more than one doses, [sic] wherein the doses are ranged from about 3 X 10^6 to about 5 X 10^{12} PFU or from about 3 X 10^8 to about 4 X 10^{11} PFU of virus per square meter of body surface area . . . . For sensitization, a virus dose is from 1 X 10^8 to about 2.4 X 10^{10} PFU/m^2, which indicates the desensitization is not limited to use one dose for only one time. After sensitization, additional virus doses of 3 X 10^8 to about 4 X 10^{12} PFU/m^2 are given to the patients. The sequential doses given after the initial desensitization dose are considered to be the equivalent to the claimed sequential desensitization does [sic] and escalated doses, because the activity served by the sequential administrations of the virus is inherent regardless what it is names artificially.

(Office Action, paragraph 22; double underlining added) Applicants respectfully disagree. Even if a disclosure says that multiple doses within a range can be administered to a subject, this does not disclose or suggest the administration of at least three sequentially increasing dose levels to a subject. The cited references, at most, only disclose administering two dose levels to a subject.

Additionally, the Examiner states,

> Pecora et al. teach a method for treating tumor with a replication-competent strain of New Castle Disease virus (PV701),, [sic] wherein one of them named ' **Desinsitizing regiment"** [sic] also comprises five dosages. The first dose is given at 12X 10^9 PFU/m^2 (desensitizing dose) on the first day followed by two doses of 24 X 10^9 PFU/m^2, two doses of 48 X 10^9 PFU/m^2, two doses of 72 X 10^9 PFU/m^2, two doses of 96 X 10^9 PFU/m^2 or 144 X 10^9 PFU/m^2. For each patient, all three doses were administrated within 1 week and repeated every 28 days intravenueously [sic]. Another one is named as two-week regiment [sic], it comprises more than one doses [sic] of NDV virus administrations, i.e. a first sensitizing does [sic] is 12 X 10^9 PFU/m^2 followed by five doses of 96 X 10^9 PFU/m^2, or five doses of 120 X 10^9 PFU/m^2, wherein the dose 2 was given 4 days

> after does [sic] 1, the patients were given three doses per week for 2 weeks followed by 1 week of treatment. Regardless whether the initial two dosages are named as an [sic] desensitization doses and the following higher dosages are named as escalated dosages, the treatment regiments [sic] meet the limitations of the claimed method. Regarding the precise dose used each time, the broad interpretation of claims 1-12, 17, 21-23, 33, 34 still read on the prior art.

(Office Action, paragraph 27; double underlining added.) Applicants respectfully disagree. As described by the Examiner, Pecora *et al.* relates to administration of a first dose of virus followed by subsequent doses of virus, wherein the subsequent doses of viruses all have the same amount of virus, but differ from the amount of virus in the first dose. Therefore, since the virus in Pecora *et al.* is clearly administered to each subject in only two different amounts, whereas the subject matter of the present claims require, *inter alia*, the administration of three different amounts to a subject, Pecora *et al.* does not anticipate the claimed invention.

With regards to Lorence '00, the Examiner states,

> using IV desensitization, the dose is from 3X 10^8 followed by 1X 10^9 PFU/m^2. [sic] 2.5X 10^9 PFU/m^2, [sic] 5 X 10^9PFU/m^2 <u>and</u> 1X 10^{10} PFU/m^2 respectively (Example 18). To this context, the claims 1-12, 17,21-23, 33, 34 [sic] all within the ranges as claims broadly drafted.

(Office Action, paragraph 31; underlining added) Applicants respectfully disagree. The underlined "and" in the previous quote from the Office Action should be an "or". For example, Table 17 of Lorence '00 summarizes the regimen of Example 18 of Lorence '00 and shows that no individual mouse received three doses, each with different amounts of virus, which is required by the present claims. In addition to Example 18, the Examiner also mentions Examples 19, 28 and 29 of Lorence '00. However, these examples disclose administration to a subject of no more than two different amounts of virus and therefore do not anticipate the present claims.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-6, 9, 12, 17, 21-23, 26-30 and 34 under 35 U.S.C. § 102.

B. Rejections Under 35 U.S.C. § 103(a)

To establish a *prima facie* case of obviousness, the Examiner must show that the references upon which she or he relied teach or suggest every limitation of the currently claimed invention. (*In re Royka*, 490 F.2d 981, 985 (Fed. Cir. 1974).)

As discussed above, none of the documents cited in the current Office Action to support an obviousness rejection disclose or suggest the following feature of the claim:

> at least one cycle comprises administering sequentially two or more desensitization doses of the virus [to a subject] followed by administering one or more escalated doses of the virus, wherein . . . the amount of the virus in the second and any subsequent desensitization dose is greater than the amount of the virus in the preceding desensitization dose; and the amount of the virus in each of the one or more escalated doses is higher than the amount of virus in each of the desensitization doses.

Therefore, based on the cited references a *prima facie* case of obviousness has not been made.

Additionally, the Examiner states that "[e]ffective dosage and schedules for administering the virus may be determined empirically, and making such determinations is within the skill in the art". (Office Action, paragraphs 23 and 28.) Applicants assume the Examiner makes reference to this as a support that the claimed dosage schedule is obvious. Applicants disagree. Following this logic, any dosage schedule for administering a virus would be considered obvious, no matter how novel or complicated the dosage schedule is. This is clearly not the law with regards to 35 U.S.C. 103(a). The Examiner is required to show that one skilled in the art at the time of the invention would have been motivated to administer a negative –stranded RNA virus to a subject as is particularly claimed.

Assuming, *arguendo*, that all of the elements of the claims were known in the art at the time of the invention, the results obtained by the claimed invention were unexpected. Example 1 and Table 3 of Applicants' specification show that the claimed invention unexpectedly results in less toxicity as compared to "single-step desensitization". The Examiner has not pointed to anything known in the art at the time of the invention that would have suggested or predicted the resulting significant reduction in toxicity, *e.g.*, as shown in Table 3 of Applicants' specification.

In summary, (i) the documents cited by the Examiner in the current Office Action do not teach all of the elements; (ii) at the time of the invention, there would have been no motivation to arrive at the claimed invention; and (iii) embodiments of the claimed invention resulted in an unexpected reduction in toxicity to the subject. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-5, 6, 9, 12, 17, 21-23, 26-30 and 34 under 35 U.S.C. § 103(a).

III. OBVIOUSNESS-TYPE DOUBLE PATENTING

Applicants appreciate and acknowledge that the Examiner has withdrawn the non-statutory obviousness-type double patenting rejection of claims 1-5 and 34 over claim 1 of U.S. Patent No. 7,056,689 in view of Lorence '94. (Office Action, page 7.)

A. Specific Non-Statutory Obviousness-Type Double Patenting Rejections

Claims 1-6, 26, 27, 29, 30 and 34 have been provisionally rejected for obviousness-type double patenting over claims 1-7 and 11-12 of copending Application No. 10/547,654 ('654 application) in view of WO 94/25627A1.[2] (Office Action, page 3.) If the Examiner maintains this rejection, Applicants will consider filing a Terminal Disclaimer upon indication of otherwise allowable subject matter.

Claims 1-6, 9, 12, 17, 21-30 and 34 have been provisionally rejected for obviousness-type double patenting over claims 1-9, 14-15 and 18-19 of copending Application No. 10/548,057 ('057) in view of WO 94/25627A1. (Office Action, page 4.) Applicants respectfully disagree. Claims 1-9, 14-15 and 18-19 of Application No. 10/548,057 do not describe or suggest administering at least three sequentially increasing dose levels of virus to a subject as required by

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[2] Applicants note that the Examiner implies that the '654 application discloses "one or more escalated doses for up to 7X 10^8PFU or 2X 10^8 PFU". (Office Action, paragraph 6.) Applicants respectfully disagree. For example, the '654 application states "the dose to be administered at a rate of up to 7.0 x 10^8 PFU per square meter of patient surface area in any ten minute sampling time period within the administration period." (the '654 application, page 3, lines 13-15; underlining added.) The "2 x10^8 PFU" in the '654 is referred to in the same way. Therefore, the 7x10^8 PFU and 2x10^8 PFU amounts refer to infusion rates, not total amounts of virus per dose.

the presently claimed invention. Also, see relevant discussions related to anticipation and obviousness in Section II above.

Claims 1-5, 29, and 34 have been provisionally rejected for obviousness-type double patenting over claims 13 and 16-17 of copending Application No. 10/700,143 in view of WO 94/25627A1. (Office Action, page 5.) Applicants respectfully disagree. Claims 13 and 16-17 of Application No. 10/700,143 do not describe or suggest administering at least three sequentially increasing dose levels of virus to a subject as required by the presently claimed invention. Also, see relevant discussions related to anticipation and obviousness in Section II above.

Claims 1-4 and 34 have been provisionally rejected for obviousness-type double patenting over claims 118-120, 133, 149 and 150 of copending Application No. 10/167,652 in view of WO 94/25627A1.[3] (Office Action, page 6.) Applicants respectfully disagree. Claims 118-120, 133, 149 and 150 of copending Application No. 10/167,652 do not describe or suggest administering at least three sequentially increasing dose levels of virus to a subject as required by the presently claimed invention. Also, see relevant discussions related to anticipation and obviousness in Section II above.

Claims 1-5 and 34 have been provisionally rejected for alleged obviousness-type double patenting over claims 157, 166, 174, 197-200, 201, 210, 217 and 230-232 of copending Application No. 09/958,809[4] in view of WO 94/25627A1. (Office Action, page 6.) Applicants respectfully disagree. Claims 157, 166, 174, 197-200, 201, 210, 217 and 230-232 of copending Application No. 09/958,809 do not describe or suggest administering at least three sequentially increasing dose levels of virus to a subject as required by the presently claimed invention. Also, see relevant discussions related to anticipation and obviousness in Section II above.

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[3] Applicants note that in the current Office Action the Examiner has not provided any details as to the reasons for rejecting claims 1-4 and 34 on the ground of non-statutory obviousness-type double patenting over claims 118-120, 133 and 149-150 of Application No. 10/167,652. Applicants believe this may have been unintentional since paragraphs 16 and 19 of the Office Action are the same. If the Examiner maintains this rejection, Applicants request further explanation with regards to the rejection.

[4] The Office Action refers to 09/985,809, but Applicants assume this is a typo and should refer to 09/958,809.

For all of the current obviousness-type double patenting rejections, except those related to Application No. 10/167,652,[3] the Examiner states that "[a]bsence unexpected result to the contrary, the claimed method is still considered as prima facie obvious absence unexpected results." (Office Action, paragraphs 11, 13 and 18; underlining added.) In Section II, above, Applicants describe embodiments of the claimed invention resulting in advantageous and unexpected results. Therefore in light of the unexpected results and/or the arguments herein, the claimed invention is neither anticipated nor rendered obvious by the cited claims of the cited co-pending applications.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the obviousness-type double patenting rejections.

B. Examiner's Statements Related To Obviousness-Type Double Patenting

In this subsection, Applicants address a few statements made in the obviousness-type double patenting section of the Office Action. The Examiner states that "[t]he double patenting rejection is not directed to a regiment [sic] that utilizes two-step desensitization prior to the escalated doses." (Office Action, paragraphs 5 and a similar statement at paragraph 12.) Applicants are unclear as to the meaning of this sentence and respectfully request clarification if the relevant obviousness-type double patenting rejections are maintained. As discussed herein, the subject matter of the present claims does relate, *inter alia*, to a regimen that utilizes two-step desensitization[5] prior to the escalated dose(s).

Further, the Examiner states that,

> [r]egarding the argument that any subsequent desensitization dose is greater then [sic] amount of the virus in the preceding desensitization dose, and the mount [sic] of virus in each of the escalated doses are higher [sic] the amount of virus in each of the desensitization dose, such limitations are not in the rejected claims.

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[5] At the end of paragraphs 21, 26 and 29 of the Office Action, the Examiner incorrectly characterizes Applicants previous statements by stating "the cited references disclose, at most, only two-step desensitization." (underlining added.) However, Applicants stated that "[t]he cited references disclose, at most, only a one-step desensitization regimen." (Applicants' Reply of April 30, 2007, page 9; underlining added.)

(Office Action, paragraphs 8 and 14.) Applicants note that the "limitation" described by the Examiner is almost word for word recited in claim 1 with only a few differences. Therefore, Applicants are unclear as to the relevance of the statement and request clarification, if the relevant obviousness-type double patenting rejections are maintained.

Conclusion

It is not believed that extensions of time are required beyond those that may otherwise be provided for herein or in accompanying documents. However, if additional extensions of time are necessary to prevent abandonment of this application, The United States Patent and Trademark Office is hereby authorized to charge any fee deficiency required to prevent abandonment of the current application or credit any overpayment to Deposit Account 50-1677.

Applicants believe that a full and complete Reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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